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ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,664	RASHTCHIAN ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-23,26,28-31,33,35,37-39,44-47,54,55,57 and 59* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 10-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 8, 9,26, 28-31, 33, 35, 37-39, 44-47, 54-55, 57, 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Currently, claims 1-3, 5-23, 26, 28-31, 33, 35, 37-39, 44-47, 54-55, 57, 59 are pending in the instant application. Claims 6, 7, and 10-23 are withdrawn from consideration as being drawn to non elected species. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejection not reiterated is hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow, where appropriate. This action is NON-FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 5, 8, 9 and 25 under 35 USC 112/first paragraph, made at section 5 of the previous office action is moot in view of the amendments to the claims.

4. The rejection of claim 36 under 35 USC 103(a) made at section 13 of the previous office action is moot in view of the cancellation of claim 36.

5. The rejections made under 35 USC 102 and 103 in the previous office action as anticipated by or unpatentable over the teachings of Vizard are withdrawn in view of the claim amendments and the new grounds of rejection set forth below.

Election/Restrictions

6. Applicant's election with traverse of the species of Taq polymerase in the reply filed on 4/11/2005 is acknowledged. The traversal is on the ground(s) that the elements added to the independent claims represent an incorporation of elements from dependent claims which have

been examined and that the claims reciting each of the allegedly distinct polymerases have been pending since the application was first filed. These arguments have been thoroughly reviewed but were not found persuasive. As stated by applicants, the claims were amended to include the limitations of the compositions containing a nonionic detergent and to stability requirements concerning storage at 20-25 deg. C. While these limitations were previously dependent from claims 2 or 3, the claims directed to the different polymerases did not require these limitations the claims directed to a polymerase were separately dependent from claims 2 or 3. As such, the search for each polymerase did not previously require a search for the limitations to the instantly amended claims. The amendment to include the limitations in claim 2 and 3 has significantly increased the search burden for each separate polymerase required to identify art to meet the limitations of claims 5-23, as now pending. With regard to applicants arguments that the previous restriction requirement (dated 11/18/2002) was withdrawn as the examiner had indicated that those claims had been previously searched, it is noted that the claims in question were identical in scope to those that had been previously searched, which is not the case for the instant claims. The scope of the claims has been amended such that the burden for searching each individual polymerase has significantly increased. The search required to identify appropriate prior art is not solely dependent on "key word searching". The search requires extensive analysis of each patent or reference in the non patent literature to determine whether the compositions meet the limitations set forth in the claims as now amended.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

7. Claims 33, 35, and 37-39 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims fail the infringement test, see MPEP 608.01(n) III.

Composition and kit claims 1-3, 30 and 31 were amended to recite "wherein said reagents are present in said composition at concentrations for performing said methods without dilution". Method claims 33, 35, and 37-39 depend from claims 2 or 3. When the compositions are used for the recited methods, claims 33, 35, and 37-39, nucleic acids would be required to be added in the form of template nucleic acids and primer(s). Once added, the resulting composition for use in the method would be less concentrated, and thus diluted. Accordingly, the claims fail the infringement test as infringement on the practice of the methods of claims 33, 35, and 37-39 would not necessarily appear to infringe on the compositions of claims 2 or 3.

Claim Rejections - 35 USC § 112

8. Claims 1-3, 5-23, 26, 28-31, 33, 35, 37-39, 44-47, 54-55, 57, 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 30 and 31 were amended to recite "wherein said reagents are present in said composition at concentrations for performing said methods without dilution" because it is unclear how the compositions would not be diluted when used to perform the methods set forth

in the claims. The specification provides no definition, direction or example of how the compositions can be used in nucleic acid synthesis, amplification, sequencing, or restriction digestion without dilution if they don't contain any nucleic acid molecules. The compositions are specifically recited to exclude nucleic acid molecules, however the claim specifically states that they would be used in a recited method. However, when the compositions are used for the recited methods, claims 33, 35, and 37-39, nucleic acids would be required to be added in the form of template nucleic acids and primer(s). Once added, the resulting composition for use in the method would be less concentrated, and thus diluted. Consequently, the metes and bounds of the recitation "without dilution" is unclear. It is unclear if the term is meant to indicate that some dilution will take place when the nucleic acid molecules are added to practice the methods in the claim. If this is the case, the specification provides no guidance as to what the metes and bounds of the change in concentration could be and still satisfy the claimed recitation. It is unclear if the recitation is meant to indicate that methods could be performed with the concentration of the components as present in the composition (for example, a composition comprising Taq at 25 U/ml with no nucleic acids, but once nucleic acid and primer are added, concentration would be diluted. However, the method could be performed with Taq at 25 U/ml, had nucleic acid and primer been present in the composition). Alternatively, it is unclear if the recitation is meant to indicate that no change in concentration would occur. If this is the case, it is unknown how the compositions without nucleic acids would be used for the recited methods, claims 33, 35, and 37-39, if they don't contain nucleic acid molecules. Neither the specification, nor claims 33, 35, and 37-39 provide any guidance as to how to accomplish the methods of claims 33, 35, and 37-39, while still meeting the limitations of the claimed compositions, from which these methods

depend. Accordingly, the metes and bounds of the components and concentrations of the claimed compositions is unclear.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 44, and 54 are rejected under 35 USC 102(b) as being anticipated by Scalice.

Scalice teaches a composition containing Taq DNA polymerase (50 U/mL), Tris buffer with MgCl, Nonidet P-40 nonionic surfactant, Tween (53-54), and an antibody (claim 44) which binds to Taq polymerase (see col. 15, lines 42-55). The recitation of "wherein said reagents are present in said composition at concentrations for performing said methods without dilution" is considered an intended use of the claimed composition and does not distinguish the claimed composition from that of Scalice because the composition of Scalice could be used to perform the methods without dilution. Further, the recitation does not result in a structural difference between the claimed composition and the composition of Scalice. Scalice inherently teaches the limitation of "wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C" because the

composition of Scalice and the broadly claimed composition are the same and therefore have the same characteristics. Additionally, non ionic detergents are known to stabilize enzymes, therefore the claimed recitation of enzymatic activity (stability) is considered an inherent property of the composition of Scalice.

Response to arguments

11. The response traverses the rejection. The response asserts that Scalice discloses a 2.5X concentrate that is diluted prior to sue, and that the reagents in the Scalice composition are not at a concentration for performing the intended nucleic acid manipulations. This argument has been thoroughly reviewed but was not persuasive. The claims are directed to compositions, not to methods. The way that Scalice uses the compositions does not distinguish the composition of Scalice from that of the claimed compositions because the intended use for a composition is given no weight when the use does not provide for a structural difference between the claimed composition and that of the prior art. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). The instant specification exemplifies that compositions containing between .01 and 1% non ionic detergents are stable (see page 32, and table 3) [wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C] and used in PCR, and teaches compositions comprising Taq preferably

contain .1-200 units per ml (see page 24). Additionally, it is known that nonionic detergents stabilize enzymes and are used in enzyme dilution buffers. Therefore, the office has reason to expect that the properties of the composition of Scalice are the same as those of the claimed composition. As stated in the MPEP in chapter 2100:

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

The way that Scalice uses the composition after it is made does not change the properties of the composition itself, which are inherent. The intended use limitations set forth in the claims do not distinguish the claimed composition from the composition taught by Scalice. For these reasons and the reasons already made of record, the rejection is maintained.

12. Claims 1, 2, 5, 26, 28, 30, 33, 54, 55, and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by Gelfand (Gelfand et al; US Patent 5,618,703).

With regard to instant claims 1 and 2, Gelfand teaches (see col. 31, lines 18-29) a master mix composition containing rTth DNA polymerase (294 units per ml), dNTP's (235 micromolar) (instant claim 28), at least one buffer salt (Tris HCL with KCL, also MnCl2) and Tween 20 (nonionic detergent) (instant claims 54, 55, and 57), wherein the composition contains no nucleic acid molecules. Gelfand teaches that for consistency and to avoid pipeting errors, this composition was prepared as a master mix containing 425 microliters, which could be used for 25 reactions at 17 microliters per reaction.

With regard to instant claims 1, 2, and 5, Gelfand teaches (see col 28, lines 1-25) reaction mixes containing Taq polymerase (which comprises Taq buffer, Taq diluent which contains the non ionic detergents Tween-20 and Nonidet P-40, dNTPs; see col. 27, lines 7-12, lines 60-67, and cols 23-24) or Pol I. These compositions were used in reactions where final compositions were made comprising the above components with and without nucleic acids (template and primer were added as a mixture). Annealing buffer was added in place of nucleic acids in reaction mixtures that lacked nucleic acids. Gelfand teaches that salt was added to the Taq reaction mixture lacking nucleic acids, such that the final concentration was 0.7mM $MnCl_2$ or 2mM $MgCl_2$ (instant claim 26). Additionally, in Example IV, cols 29-30, Gelfand teaches different Taq reaction mixtures (94 kDa Taq, as well as Taq Stoffel fragment) which lack nucleic acids. These mixtures were made to comprise dNTP, diluent which contains the non ionic detergents Tween-20 and Nonidet P-40, enzyme (94 kD Taq or Stoffel fragment), and High salt buffer or low salt buffer (see col 24). These mixtures were used in reactions where final compositions were made comprising the above components with and without nucleic acids. Annealing buffer was added in place of nucleic acids in reaction mixtures that lacked nucleic acids.

With regard to instant claim 33, Gelfand teaches that this composition was used in amplification (see col. 32, lines 1-8). With regard to instant claim 30, Gelfand teaches that the compositions can be provided in kit format (col 22). Further, it is noted that the instantly claimed kits provide no structural difference from a composition contained in a container, which is inherently taught by Gelfand. Therefore, even absent a teaching of kits, the composition of Gelfand which was inherently contained in a tube, anticipates the instantly claimed kit.

The recitation of "wherein said reagents are present in said composition at concentrations for performing said methods without dilution" is considered an intended use of the claimed compositions and does not distinguish the claimed compositions from that of Gelfand because the compositions of Gelfand could be used to perform the methods without dilution. Further, the recitation does not result in a structural difference between the claimed composition and the composition of Gelfand. Gelfand inherently teaches the limitation of "wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C" because the compositions of Gelfand and the broadly claimed composition are the same and therefore have the same characteristics. Additionally, non ionic detergents are known to stabilize enzymes, therefore the claimed recitation of stability is considered an inherent property of the compositions taught by Gelfand.

Claim Rejections - 35 USC § 103

13. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand (Gelfand et al; US Patent 5,618,703).

Gelfand teaches (see col 28, lines 1-25) reaction mixes containing Taq polymerase (which comprises Taq buffer, Taq diluent which contains the non ionic detergents Tween-20 and Nonidet P-40, dNTPs; see col. 27, lines 7-12, lines 60-67, and cols 23-24). The reaction mix was made from a 12X master mix of Taq which contained 12 units of enzyme. The composition was used in reactions where final compositions were made comprising the above components with and without nucleic acids (template and primer were added as a mixture). Annealing buffer was added in place of nucleic acids in reaction mixtures that lacked nucleic acids. Gelfand teaches

that 10 different aliquots were taken from the 12X Taq master mix and used in for different reactions including the reaction mix which lacked template and primer (col. 28). Although Gelfand does not teach the specific reaction volumes for the RT reactions in this example, Gelfand teaches that RT reaction volumes should be 20 uL per sample (see col.35, line 22). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used 20 uL samples in the reverse transcription reactions taught by Gelfand because Gelfand teaches that such is a volume which should be used for such reactions. Given that the 12X mix contained at least 10 aliquots, a single aliquot of 10 total aliquots would contain 1.2 units of Taq in 20uL reaction volume, that is 60 units/ml of enzyme in the reaction mix lacking template and primer.

14. Claims 1-2, 5, 8-9, 26, 28, 30, 33, 54, 55, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen (Olsen et al; WO 95/00664) in view of Sobol, and Gelfand (Gelfand et al; US Patent 5,618,703).

Olsen teaches performing multiple PCR reactions using different primer pair and templates to identify primer pairs suitable for detection of Salmonella species in samples (see para bridging pages 2-3; page 7, first full para; page 14, last para). Olsen teaches that the PCR reactions contained 105 uL comprising template DNA, 50mMKCL, 2.5 mM $MgCl_2$ (instant claim 26), 10 mM Tris, 200uM each dNTP (instant claim 28), 0.5% Tween, and 2.5 units of Taq polymerase (23.8 U/ml). While Olsen teaches that template was added to the PCR mixture, Olsen is silent with regard to the steps of making of the composition prior to template addition.

However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes PCR reagents, including polymerase, other than primers and template. Sobol exemplifies methods wherein the PCR master mix is aliquoted to different reaction tubes where the reagents are present at concentrations where the methods could be performed without dilution (about 14 U/ml of Taq polymerase). In the method exemplified by Sobol, 1 uL of primer and 10 uL of template was added to each tube, providing minimal dilution of the PCR master mix. It is well known to those of skill in the art that a master mix is typically employed when performing multiple reactions in order to improve efficiency and consistency and to avoid pipetting error. For example, Gelfand teaches methods of performing multiple reverse transcription reactions wherein all reagents are added in a master mix containing a thermostable polymerase, such as Taq, a nonionic detergent, all 4 dNTPs, and a buffer salt where the reagents are present at concentrations where the methods can be performed without dilution (see cols 27, 28, 30 and 31). Gelfand specifically teaches a method wherein multiple samples were analyzed and "for consistency and to avoid pipetting errors" the mix was prepared as a master mix and aliquoted as 17 uL into different reaction tubes such that only a single uL of primer and 2 uL of template were added (see col. 31). Gelfand also teaches packaging compositions in kit format (col 22). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the multiple PCR methods using different primers and template of Olsen with the use of a master mix containing all reagents necessary for the reaction except for primer and templates where the reagents are present at dilute concentrations such that the methods could be performed without dilution, as taught by Sobol and Gelfand, for the purpose of increasing the consistency and to

reduce pipetting errors in the reactions of Olsen. The ordinary artisan would have been motivated to use a master mix as taught by Sobol and Gelfand because Sobol and Gelfand each exemplify the ease of use of a master mix composition when different multiple reactions require analysis using different templates and primers, and Gelfand specifically teaches that the use of such master mixes can improve consistency and reduce pipetting errors. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, requiring the addition of a relatively small amount of primer and template and thus could be used in any amplification reaction. In performing the improved method of Olsen in view of Sobol and Gelfand, the ordinary artisan would have arrived at a master mix composition which would require the addition of as little as a uL of primer and 5 uL of DNA template. For a 105 uL volume total reaction volume, the concentration of Taq polymerase would be about 25 U/ml in the master mix. The recitation of "about 20 U/ml" in claim 9 has been broadly interpreted to encompass 25 U/ml. With regard to the limitation of "wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C", such is considered a property of the claimed composition. As the composition taught by Olsen in view of Sobol and Gelfand is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. It would have been further prima facie obvious to provide the composition of Olsen in view of Sobol and Gelfand in a "kit" for the obvious improvement of providing a premade composition for ease of use.

15. Claims 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen in view of Sobol and Gelfand as applied to claims 1-2, 5, 8-9, 26, 28, 30, 33, 54, 55, and 57 above, and further in view of Scalice.

The teachings of Olsen in view of Sobol and Gelfand are set forth above. Olsen in view of Sobol and Gelfand does not teach an antibody which specifically binds to the thermostable polymerase. However Scalice teaches that the use of antibody specific for a thermostable DNA polymerase, such as Taq, can be used to reduce or eliminate the formation of non specific products in PCR methods (see abstract). Scalice teaches that the enzyme and antibody can be supplied and used in a mixture with other PCR reagents, or that the enzyme and antibody can be supplied and added separately, or mixed together just prior to use (see col. 10,lines 23-38) Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have improved the PCR compositions/kits of Olsen in view of Sobol and Gelfand with the use of an additional component, an antibody specific for Taq polymerase as taught by Scalice. The ordinary artisan would have been motivated to add an antibody specific for Taq polymerase to the PCR mixtures/kits of Olsen in view of Sobol and Gelfand because Scalice teaches that such antibody can be used to reduce or eliminate the formation of non specific products in PCR methods. The ordinary artisan would have been motivated to add the antibody to the mixture/kit of Olsen in view of Sobol and Gelfand for the purpose of providing all necessary reagents other than primer and template for use in any PCR reaction. Alternatively, the ordinary artisan would have been motivated to provide the antibody in a kit in a separate container to provide the user with added flexibility should a specific reaction not require the use of the antibody.

16. Claims 1-3, 5, 8, 26, 29-31, 33, 35, 54, 55, 57, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soderlund in view of Sobol and Gelfand (Gelfand et al; US Patent 5,618,703).

Soderlund teaches DNA sequencing methods for routine determinations of point mutations and specific nucleotide variations in any DNA template, utilizing specific detection primers, whose identity is dependent on the variation to be detected (see page 3, para 20-23). Soderlund teaches that reactions mixtures can contain at least one dNTP and at least one ddNTP (see para 55-59). Soderlund teaches that the methods can also be used to detect more than variation in an immobilized target and teaches dividing a sample into 2, each sample containing one primer, such that two variations could be detected on the same target (see page 7, para 60). Soderlund generally teaches that reagents can be packaged in kits and provided individually, or in different combinations (see para 0062). Soderlund exemplifies a 50 uL reaction mixture containing 2 units of Taq polymerase (40 U/ml), a dNTP, a ddNTP (.8 uM), 1.5 mM $MgCl_2$, and 0.1% Tween.

Although Soderlund does not specifically teach a composition that does not contain nucleic acids, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes PCR reagents, including polymerase, other than primers and template. Sobol exemplifies methods wherein the PCR master mix is aliquoted to different reaction tubes where the reagents are present at concentrations where the methods could be performed without dilution (about 14 U/ml of Taq polymerase). In the method exemplified by Sobol, 1 uL of primer and 10 uL of template was added to each tube, providing minimal dilution of the PCR master mix. It is well known to those

of skill in the art that a master mix is typically employed when performing multiple reactions in order to improve efficiency and consistency and to avoid pipetting error. For example, Gelfand teaches methods of performing multiple reverse transcription reactions wherein all reagents are added in a master mix containing a thermostable polymerase, such as Taq, a nonionic detergent, all 4 dNTPs, and a buffer salt where the reagents are present at concentrations where the methods can be performed without dilution (see cols 27, 28, 30 and 31). Gelfand specifically teaches a method wherein multiple samples were analyzed and "for consistency and to avoid pipetting errors" the mix was prepared as a master mix and aliquoted as 17 uL into different reaction tubes such that only a single uL of primer and 2 uL of template were added (see col. 31). Gelfand also teaches packaging compositions in kit format (col 22). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the methods of detecting different nucleotide variations in different targets of Soderlund, using different detection primers, with the use of a master mix containing all reagents necessary for the reaction except for primer and templates where the reagents are present at dilute concentrations (such that the methods could be performed without dilution), as taught by Sobol and Gelfand, for the purpose of increasing the consistency and to reduce pipetting errors in the sequencing methods of Soderlund. The ordinary artisan would have been motivated to use a master mix as taught by Sobol and Gelfand because Sobol and Gelfand each exemplify the ease of use of a master mix composition when different reactions require analysis using different templates and primers, and Gelfand specifically teaches that the use of such master mixes can improve consistency and reduce pipetting errors. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primer and

template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, requiring the addition of a relatively small amount of primer and template and thus could be used to sequence a large number of different nucleotide variations. With regard to the limitation of "wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C", such is considered a property of the claimed composition. As the composition taught by Soderlund in view of Sobol and Gelfand is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. It would have been further prima facie obvious to provide the composition of Soderlund in view of Sobol and Gelfand as a "kit" for the obvious improvement of providing a premade composition for ease of use.

17. Claims 1-2, 5, 8-9, 26, 28, 30, 33, and 37-39, 54, 55, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes in view of Hoeltke (Hoeltke et al; US Patent 5,814,502) and further in view of Sobol and Gelfand.

Barnes teaches compositions for nucleic acid amplification comprising, for example, Klentaql, which is exonuclease free, or Taq, a salt buffer which contains magnesium (3.5 mM) and 250 μM dNTPs (page 2217, col. 1, para 2). Barnes teaches that the compositions were used to amplify long nucleic acids (claim 33) larger than 8 kb (claims 37-39). Barnes does not teach the compositions comprising a nonionic detergent, however Hoeltke teaches that nonionic detergents such as Triton X-100, Tween, Brij-35, and NP40 stabilize polymerases such as Taq (see col. 2, lines 45-54). Additionally, Gelfand teaches that detergents such as Tween–20 and

Nonidet P-40 are present in enzyme dilution buffers and teaches reaction mixtures should be employed where they are preferably present at a final concentration of between 0.01-.1% (col. 19, lines 50-55). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the reaction mixture of Barnes to include a non ionic detergent for the purpose of stabilizing the reaction mixture of Barnes, as taught by Hoeltke. Further, it would have been prima facie obvious to one of ordinary skill in the art to include the use of a non ionic detergent in the composition of Barnes because Gelfand teaches that such are present in enzyme dilution buffers. Although Barnes in view of Hoeltke does not specifically teach a composition that doesn't contain nucleic acid molecules, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes PCR reagents, including polymerase, other than primers and template. Sobol exemplifies methods wherein the PCR master mix is aliquoted to different reaction tubes where the reagents are present at concentrations where the methods could be performed without dilution (about 14 U/ml of Taq polymerase). In the method exemplified by Sobol, 1 uL of primer and 10 uL of template was added to each tube, providing minimal dilution of the PCR master mix. It is well known to those of skill in the art that a master mix is typically employed when performing multiple reactions in order to improve efficiency and consistency and to avoid pipetting error. For example, Gelfand teaches methods of performing multiple reverse transcription reactions wherein all reagents are added in a master mix containing a thermostable polymerase, such as Taq, a nonionic detergent, all 4 dNTPs, and a buffer salt where the reagents are present at concentrations where the methods can be performed without dilution (see cols 27, 28, 30 and 31). Gelfand specifically teaches a method wherein multiple samples

were analyzed and "for consistency and to avoid pipetting errors" the mix was prepared as a master mix and aliquoted as 17 uL into different reaction tubes such that only a single uL of primer and 2 uL of template were added (see col. 31). Gelfand also teaches packaging compositions in kit format (col 22). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the methods of amplification of different targets of Barnes in view of Hoeltke with the use of a master mix containing all reagents necessary for the reaction except for primer and templates where the reagents are present at dilute concentrations such that the methods could be performed without dilution, as taught by Sobol and Gelfand, for the purpose of increasing the consistency and to reduce pipetting errors in the reactions of Barnes in view of Hoeltke. The ordinary artisan would have been motivated to use a master mix as taught by Sobol and Gelfand because Sobol and Gelfand each exemplify the ease of use of a master mix composition when different multiple reactions require analysis using different templates and primers, and Gelfand specifically teaches that the use of such master mixes can improve consistency and reduce pipetting errors. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primer and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, requiring the addition of a relatively small amount of primer and template and thus could be used in to amplify an long nucleic acid target. With regard to the limitation of "wherein said thermostable enzyme retains at least 90% of its enzymatic activity for at least 4 weeks when said composition is stored at about 20 to 25 deg. C", such is considered a property of the claimed composition. As the composition taught by Barnes in view of Hoeltke and further in view of

Sobol and Gelfand is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. It would have been further prima facie obvious to provide the composition of Barnes in view of Hoeltke and further in view of Sobol and Gelfand as a "kit" for the obvious improvement of providing a premade composition for ease of use.

Response to Arguments

18. Applicant's arguments directed to rejections under 35 USC 103(a), regarding references that teach compositions that contain nucleic acids, and the traversal on the basis that the skilled artisan reading these references "would be led in a direction divergent from the path that was taken by applicant", as well as arguments that such references teach away from the claimed invention, have been thoroughly reviewed but were found unpersuasive. These arguments are addressed with regard to newly applied rejections set forth above. Firstly, it is noted that rejections under 35 USC 103 directed to such references were not set forth *solely* based on the teachings of such references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Secondly, in response to applicant's argument that 'the federal circuit held that 'references that teach away cannot serve to create a prima facie case of obviousness'" citing In re Gurley (Fed. Cir. 1994), it is noted that the MPEP, chapter 2123 states, "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious

composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). In the instant rejections, Olsen and Barnes are silent with regard to order of steps needed to arrive at the specific compositions containing nucleic acid molecules. There is no teaching "away" that the compositions are required to be made in any specific way. With regard to Soderlund, Soderlund actually teaches that the primer can be hybridized to the target and that a selected nucleoside triphosphate or a mixture of such can then be added. As exemplified by the teachings of Gelfand, the practice of pre-annealing primer and template, before their addition to a reaction mixture including enzyme, detergent, and nucleoside triphosphates, was employed at the time the invention was made. As already discussed, the courts have held that "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). The rejections were not made solely based on the teachings of Olsen, Soderlund or Barnes, but employed the use of common scientific knowledge and motivation provided in the prior art when the instant invention was made.

With regard to the citation of In re Geisler,. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997), while the court held that "A prima facie case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention", the court found that the reference did not teach away. MPEP 2144.05 states "(Applicant argued that the prior art taught away from use of a protective layer for a reflective article having a thickness within the claimed range of "50 to 100 Angstroms." Specifically, a patent to Zehender, which was relied upon to reject applicant's claim, included a

statement that the thickness of the protective layer "should be not less than about [100 Angstroms]." The court held that the patent did not teach away from the claimed invention. "Zehender suggests that there are benefits to be derived from keeping the protective layer as thin as possible, consistent with achieving adequate protection. A thinner coating reduces light absorption and minimizes manufacturing time and expense. Thus, while Zehender expresses a preference for a thicker protective layer of 200-300 Angstroms, at the same time it provides the motivation for one of ordinary skill in the art to focus on thickness levels at the bottom of Zehender's suitable' range- about 100 Angstroms- and to explore thickness levels below that range. The statement in Zehender that [i]n general, the thickness of the protective layer should be not less than about [100 Angstroms]' falls far short of the kind of teaching that would discourage one of skill in the art from fabricating a protective layer of 100 Angstroms or less. [W]e are therefore not convinced that there was a sufficient teaching away in the art to overcome [the] strong case of obviousness' made out by Zehender.")." In the instant case, Sobol and Gelfand each teach master mixes with little dilution, as well as mixes where the components are present at concentrations such that the methods could be performed without dilution, and master mixes where all components but nucleic acids (primers and template) are present, and thus provide motivation for one of ordinary skill in the art to focus on such attributes of compositions. Gelfand specifically teaches that the attributes of exemplary master mixes was for "consistency and to avoid pipetting errors".

Conclusion

19. No claim is allowable over the cited prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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6/27/05